USAID
INFECTIOUS DISEASE INITIATIVE

STRATEGIES AND INTERVENTIONS TO UNDERSTAND, CONTAIN, AND RESPOND TO THE DEVELOPMENT AND SPREAD OF

ANTIMICROBIAL RESISTANCE

for more information please contact:

Tony Boni
Coordinator, USAID Antimicrobial Resistance Working Group
Tel. 202-712-4789
Fax. 202-216-3702
email aboni@usaid.gov

Updated: 5-22-00

TABLE OF CONTENTS

LIST OF ACRONYMS

AIHA	American International Health Alliance
APUA	Alliance for the Prudent Use of Antibiotics
CDC/NCID	Centers for Disease Control and Prevention/National Center for Infectious Diseases
HIID/ARCH	Harvard Institute for International Development/Applied Research on Child Health
ICDDR,B	International Centre for Diarrheal Disease Research, Bangladesh: Centre for Health and Population Research
INCLEN	International Clinical Epidemiology Network
INRUD	International Network for the Rational Use of Drugs
JHU/FHACS	Johns Hopkins University/Family Health and Child Survival
MSH	Management Sciences for Health
PAHO	The Pan American Health Organization
QAP II	Quality Assurance Project II (USAID)
RPM	The Rational Pharmaceutical Management Project (USAID)
USP	The United States Pharmacoepial Convention
WHO/CAH	World Health Organization/Child and Adolescent Health
WHO/CDS	World Health Organization/Communicable Diseases and Surveillance
WHO/HTP/EDM	World Health Organization/Health Technology and Pharmaceuticals/Essential Drugs and Medicines

INTRODUCTION

In 1998, USAID launched a new strategy to reduce the threat of infectious diseases of major public health importance[1]. This ten-year strategy focuses on four major areas: antimicrobial resistance (AMR); tuberculosis; malaria; and surveillance and response. Priorities for each of the four areas (as listed in the USAID Infectious Disease Strategy) were developed through a consultative process which involved numerous partners, including the World Health Organization, the Centers for Disease Control and Prevention, the National Institutes of Health, universities, and other institutions.

This document summarizes the AMR-related activities that have been supported by the Office of Health and Nutrition in USAID's Global Bureau using FY 1998-99 Infectious Disease funding. The activities are listed according to the Agency's priority areas for Antimicrobial Resistance: (1*) Establishing a Global Strategy and Action Plan*; (2) *Improving the Understanding of AMR*; (3) *Developing Methods to Detect AMR*; (4*) Responding to Data on AMR and Drug Use*; (5) *Preventing and Slowing the Spread of AMR*. Activities were selected by the USAID AMR Working Group based on their ability to:

- Contribute to the development of a comprehensive, evidence-based AMR strategy and action plan;
- Address both key USAID program areas (e.g. Child Survival, Maternal Health, Reproductive Health) threatened by AMR and priority diseases set forth in the USAID Infectious Disease Strategy (AMR component);
- Address priority areas identified at technical consultations (e.g. WHO's meeting on Research Strategies for Determining Antibiotic Efficacy in Childhood Pneumonia) and global consensus meetings (e.g. International Conference on Improving the Use of Medicines);
- Fill identified gaps in setting standards and implementing known interventions.

Infectious Disease activities funded by the Office of Health and Nutrition in USAID's Global Bureau encompass research, the establishment of guidelines and standards, and the development and field-testing of tools, interventions, and case-management approaches in order to address AMR and antimicrobial drug use. In contrast, country-specific implementation activities for the Infectious Disease Initiative will be primarily funded at the Mission level. It is anticipated that AMR activities supported by the Global Bureau's Office of Health and Nutrition will, in the future, assist Missions and others in designing and implementing interventions to address the problem of antimicrobial resistance in developing countries.

During the process of developing WHO's AMR Global Strategy and Action Plan, research issues will be identified and effective implementation activities will be outlined. The WHO Global Strategy and Action Plan will assist USAID in identifying priorities, coordinating activities, leveraging resources, and increasing awareness of the importance of limiting the emergence and spread of AMR.

In year one (FY98) of the USAID Infectious Disease Initiative, the main focus of research will be on resistance to drugs used to treat acute respiratory infections (ARI) which, in developing countries, are the major killers of children. AMR threatens the effectiveness of case management that is currently the primary approach to decreasing mortality from ARIs. Research will address the knowledge gaps related to the treatment of ARIs and will contribute to the process of revising treatment guidelines and drug policy when appropriate. All research studies will be externally reviewed prior to initiation.

Additional activities addressing AMR as it relates to diarrheal disease, meningitis, nosocomial (hospital-acquired) infections, and sexually-transmitted infections (STIs) will be developed in year 2 of the Infectious Disease Initiative and beyond as information from the technical reviews becomes available (see

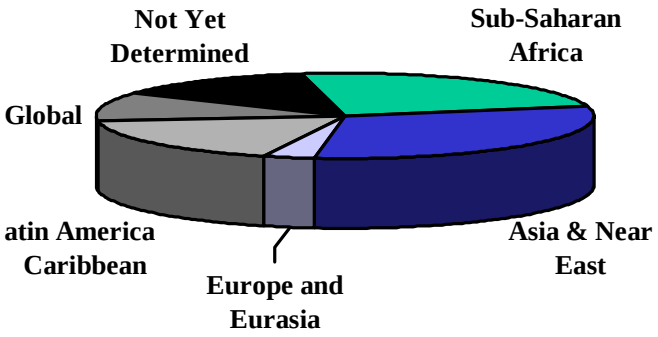
[1] For more information, visit: http://www.info.usaid.gov/pop_health/webid.htm

AMR Component 1: *Establishing a Global Strategy and Action Plan*). Surveillance of AMR, drug-resistant malaria, and drug-resistant TB are described in documents developed by the USAID Working Groups for surveillance, malaria, and TB, respectively, as such activities are within the purview of those groups.

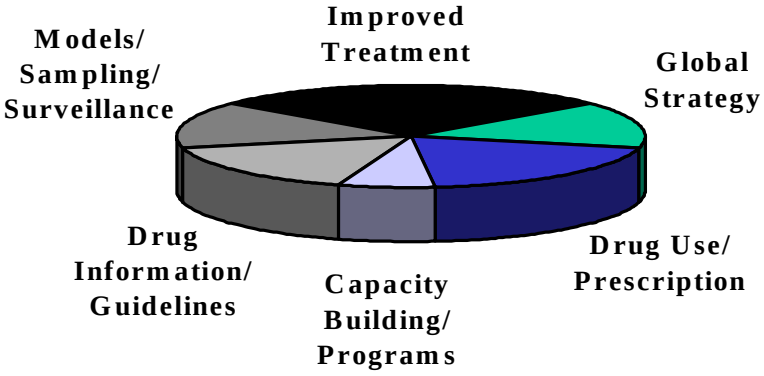
The distribution of AMR activities being supported by the USAID Global Bureau is shown below in Figure 1 and Table 1.

Figure 1. Distribution of Activities by Region, Activity Type, and Disease.

Regional Distribution (*n* = 157)



Activity Distribution (*n* = 61)



Disease Distribution (*n* = 35)

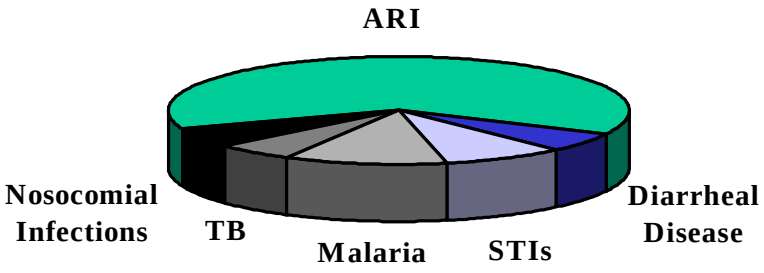


Table 1. Partner and Country Distribution

Location of Activity		APUA	CDC	HIID	JHU	MSH	QAP	USP	WHO
Not yet determined			2.6			5.4			2.2, 3.6, 5.1, 5.27
Global		1.6	3.3		1.2, 1.8	5.26		1.10	1.1,2.3,2.11,2.12, 2.13,4.1,4.2,4.3
Africa	Region		3.1, 5.17	1.7, 5.19	3.2	1.5, 1.7,1.9, 2.5, 5.19			2.7
	Benin					2.4			2.4
	Gambia			5.14					5.14
	Ghana			5.5, 5.15		5.5		1.3	5.15
	Kenya		2.10	5.5		2.4, 5.5			2.4
	Malawi		2.10				5.22		
	Mali				5.20,5.21				
	Mozambique							1.3	
	Nigeria			5.14					5.14
	South Africa			5.5, 5.10, 5.14, 5.15	2.1	2.4, 5.5			2.4, 3.4, 5.8, 5.13, 5.14, 5.15
	Tanzania					5.25			
	Uganda			5.5	5.7	2.4, 5.5			2.4
	Zambia			5.15, 5.16		2.4	5.22	1.3	2.4, 5.15, 5.16
	Zimbabwe				2.1, 5.9				4.4, 5.9
Asia and Near East	Region		3.1, 5.17	1.7, 5.19		1.5,1.7,1.9, 2.5, 5.19			2.7, 3.5
	Bangladesh			5.14, 5.16	2.1				5.12, 5.14, 5.16
	Egypt		2.14	5.14	2.1, 5.9				5.9, 5.14
	India			5.10,5.14, 5.15, 5.16	3.2, 5.9, 5.20				5.9, 5.14, 5.15, 5.16
	Indonesia			5.5, 5.14	2.1	2.4, 5.5			2.4,5.12,5.14
	Nepal		2.14	5.5	5.20	5.5		1.3, 5.3, 5.24	
	Pakistan			1.4, 5.14, 5.15, 5.16	5.9				5.8, 5.9, 5.11, 5.14, 5.15, 5.16
	Philippines			5.5, 5.14	2.1	2.4, 5.5			2.4, 5.6, 5.14
	Thailand			5.5, 5.14		5.5			5.14
	Vietnam			5.5, 5.10, 5.15		5.5			5.8, 5.15, 5.13
	Yemen			5.16					5.16
Europe and Eurasia	Region		5.17		5.9	1.5, 1.7, 1.9			5.9
	Moldova							5.23	
	Russia							1.3, 5.23	
Latin America and Caribbean	Region		3.1,5.17, 5.18	1.7, 5.19		1.5,1.7,1.9, 2.5, 5.19			2.7
	Argentina	5.2		5.14					2.8, 5.14
	Brazil			5.14	5.9				2.8, 5.9, 5.13, 5.14
	Columbia	5.2		5.15	5.9				2.8, 5.9, 5.15
	Dom. Rep.	5.2	2.9						2.8
	Guatemala				3.2, 5.8				
	Haiti				5.20				
	Mexico			5.15, 5.16					5.15, 5.16
	Paraguay								5.13
	Peru			5.10				1.3	2.8, 5.13
	Venezuela	5.2							

Some activities are underlined to indicate that their sites have not been finalized.

AMR Component 1: Establishing a Global Strategy and Action Plan

1.1: Establishing a Global Strategy and Action Plan

Implementing Organization: WHO/CAH, WHO/CDS, WHO/HTP/EDM

Description:

1. Define and maintain updated an action plan with milestones and time lines, indicating roles for partners;
2. Establish a baseline through data gathering (from existing study sites, published literature and commissioned reviews (see "*Expert Technical Reviews*" listed below) to document levels of resistance (and trends where available) in specified patient groups for priority diseases (pathogens) and data on morbidity, mortality and cost impacts of resistance;
3. Develop a framework of causal factors that favor the emergence and spread of resistance and identify elements that can be targeted for interventions;
4. Seek consensus on framework and relative importance of causal factors;
5. Document interventions that have been shown to effectively target specific elements; define the gaps in knowledge of effective interventions; prepare an inventory of research planned/underway to fill gaps; seek consensus on interventions and the knowledge gaps;
6. Encourage the testing of additional interventions;
7. Assess the cost-effectiveness/cost-benefit of interventions;
8. Develop a programme of evidence-based interventions to be implemented at country level; revise and refine as new data become available;
9. Assist Member States in the introduction and implementation of the containment strategy.

Countries/Regions: Worldwide.

Expert Technical Reviews (and Responsible Organization):

- Antimicrobial Drug Information (RPM/USP; see activity 1.3)
- ARI (CDC)
- Behavior, part I (HIID/ARCH, RPM/MSH; see activity 1.5)
- Behavior, part II (HIID/ARCH, RPM/MSH; see activity 1.7)
- Diarrheal Disease (JHU/FHACS; see activity 1.2)
- Economic Impact of AMR (Global Forum for Health Research, HIID/ARCH; see activity 1.4)
- Effects of Provider Reimbursement Mechanisms and Managed Care (RPM/MSH; see activity 1.9)
- Gonorrhea (WHO)
- Magnitudes and Trends of AMR (WHO)
- Malaria (CDC)
- Non-Human Use of Antimicrobial Drugs (WHO; see activity 2.3)
- Nosocomial Infections (JHU/FHACS; see activity 1.8)
- Role of Drug Rotation, Reserve, and Combination (WHO)
- Sentinel AMR Policy Documents (APUA; see activity 1.6)

1.2: State of the Art Technical Review of Antimicrobial Resistance of Selected Bacterial Diarrheal Diseases: Shigellosis, Cholera and Campylobacteriosis

Implementing Organization: JHU/FHACS

Description: A literature review will be conducted by at least two persons who are expert in the field of. A microbiologist will carry out the review of bacterial mechanisms of resistance and an epidemiologist/ clinician will carry out the review of antibiotic resistance in the community and health facilities. Sections of the review will include: a) a summary of basic principles and mechanisms in antibiotic resistance; b) examples of the development of epidemics due to resistant strains as well as examples (if any) of the re-emergence of sensitive strains; c) the clinical implications of case management of patients with resistant organisms including the complications to the patients being treated with inappropriate antibiotics; d) review of programs in which a more rational approach was attempted for using antibiotics in diarrhea; e) review of reasons for the continued use of inappropriate antibiotics; f) cost-effectiveness implications of antibiotic use for diarrhea; g) policy implications for the management of diarrhea.

Countries/Regions: The work will be done in Baltimore at JHU, with communications with other offices at WHO, PAHO, and international centers.

1.3: State of the Art Technical Review of Antimicrobial Drug Information

Implementing Partner: RPM/USP

Description: RPM/USP will conduct a review of the most accessible and widely-used AM drug information available in selected developing countries by hiring local consultants to collect the available professional literature, e.g., journals, newsletters, Standard Treatment Guidelines, manuals. At the same time, USP will collect drug information produced by other international organizations for use in support of health sector programs in developing countries. USP staff will review and evaluate the quality of the information, including the content of both the articles and the advertising, against generally accepted prescribing recommendations, including USP standards in drug information development. Draft versions of the country analyses, with copies of the original information reviewed, will be provided to USP's International Health Advisory Panel for further input and a request for recommendations. The International Panel will also be called upon to assist with collection of the material. Results of the review will be disseminated through WHO, USAID, FIP, INRUD and other international networks and organizations.

Countries/Regions: The state of the art review will cover 6-8 developing countries including Ghana, Mozambique, Nepal, Peru, Russia, and Zambia.

1.4: Costs and Cost-effectiveness Analysis of Antimicrobial Resistance in Developing Countries

Implementing Organizations: HIID/ARCH and Global Forum for Health Research

Description: HIID/ARCH will recruit an applied economist to serve as a focal point for the policy

analyses and research associated with this initiative. The initial activities will include the following:

1. A systematic review (leading to a published document) of the information on the costs of antimicrobial resistance at various levels of the health system. The review will include available household level data.
2. The development of a set of cost-effectiveness studies to provide information on the comparative value of specific interventions.

To be most informative, the cost-effectiveness of clinical policy development and implementation should be studied for different problems in antimicrobial use in the same setting at many levels (institutional, regional, national). However, the mediating impact of factors like professional culture, structure of the medical system, or regulatory barriers to antimicrobial access on cost-effectiveness considerations can only be studied by examining a single issue or a small number of issues in a number of country settings. Examples of clinical problems with interesting cost-effectiveness components that might be used to focus these analyses include optimal treatment approaches for managing gonorrhea; policies for the use of prophylactic antibiotics during surgery; or treatment of moderate to severe respiratory infections.

Countries/Regions: Pakistan

1.5: Review of Interventions to Improve Antimicrobial Use by Health Providers

Implementing Organizations: RPM/MSH

Description: Using explicitly-predefined criteria for appropriate study design, the review will identify: interventions that have been rigorously tested; the settings where the interventions have taken place; the methods used to improve antimicrobial use, and; whether the intervention succeeded or failed to achieve its objectives. The review will cover interventions that target antimicrobial use by health providers working in primary care facilities, hospitals, and retail drug outlets. Interventions to improve community or patient drug use behavior are beyond the scope of this review.

The review will analyze relevant studies that (a) have been previously collected for the 1997 Chiang Mai Conference on Improving Use of Medicines (ICIUM); (b) were presented at the ICIUM Conference; (c) have been published or reported since then. The INRUD bibliography database will be used to identify relevant studies not previously reviewed or reported since 1996. Through RPM collaborators in the Russian Federation and the Newly Independent States, a search will be made for studies that may have been undertaken and reported in Russian and other Eastern European languages.

Countries/Regions: Review will cover studies in Africa, Asia, Latin America, the Newly Independent States, and Eastern Europe

1.6: Synthesis of Sentinel Policy Documents Concerning Strategies for Curbing AMR

Implementing Organization: Alliance for the Prudent Use of Antibiotics

Description: APUA staff will: (1) compile the major expert policy documents produced in both industrialized and developing countries, including selected countries from the APUA Chapter Network; (2) review and develop a brief summary of individual documents; (3) create an outline of major issues and

strategies to be addressed (i.e. background on AMR--issues and needs; prevention and control of AMR--research, prevention practices, surveillance; strategies and resources to control AMR--public health strategies, resources for research and data-collection; legal, ethical, and regulatory issues related to controlling AMR; conclusions and recommendations); (4) develop a single review document identifying areas of agreement and disagreement; (5) create tables that systematically summarize the information from the major reports on AMR; (6) develop draft document that suggests priorities based on compilation of recommendations; (7) coordinate draft review by selected members of the APUA Scientific Advisory Board; (8) refine document based on committee's recommendations; (9) submit draft document to USAID and WHO for comments; (10); revise document; and (11) submit the final document to USAID and WHO for input into the process of global strategy formulation.

Countries/Regions: Not applicable.

1.7: Reviews of Antecedents of and Interventions to Decrease Inappropriate Antimicrobial Use by Health Providers and Community Members

Implementing Organizations: HIID/ARCH and RPM/MSH

Description: *Source of Materials:* These reviews would access all the material on both health provider and community-oriented interventions collected for the ICIUM conference. The INRUD bibliography would be a primary source for identifying supplementary materials, although the extensive collection on community use of antimicrobials at WHO/EDM and the University of Amsterdam would also be included. Additional search will also be performed within the Med-line, Pop-line database and also other related centers such as the one at the University of Groningen. For these reviews to be reasonably complete, a more active process of information gathering would be needed, since a large amount of useful material of determinants of use has never been published. For example, there is a substantial amount of unpublished materials on community use of antimalarials. This material gathering could be carried out through existing research networks as was done in collecting the ICIUM review materials.

Personnel: The review would be prepared by Dr. Aryanti Radyowijati and Dr. Hilbrand Haak, supervised by the staff from the ARCH project and RPM staff. The supervision covers comments on versions of the manuscript as it develops, and participation in the revision of the draft documents. A meeting will be held at the beginning of the review process to develop a detailed plan for the reviews, and during the revision process.

Timing: This review will require six months periods of person-works, divided into two steps. The first step is to gather the existing materials for the review, which is 2 person-months of work. And the second step for reading and writing the review, which is 4 person-months of work.

Countries/Regions: The review will cover studies in Africa, Asia, Latin America and the NIS

1.8: Research Priorities for the Prevention and Control of Nosocomial Infections in Developing Countries

Implementing Organization: JHU/FHACS

Description. The epidemiology, risk factors and etiology of nosocomial infections in developing countries will be reviewed. Epidemiologic information important for the control of nosocomial infections, but for which information is sparse, will be identified and specific research questions proposed. Strategies for the prevention and control of nosocomial infections in developing countries will be reviewed and the data on their effectiveness critically examined. Prevention and control strategies requiring further research will be identified. The emergence and spread of antibiotic-resistant bacteria within health care settings, and strategies to control antibiotic resistance, will also be considered. The review will focus on the epidemiology and control of nosocomial infections in health centers and district hospitals. The use of antibiotics outside health care facilities or in animal husbandry will not be considered in this review.

Countries/Regions: Not applicable.

1.9: Review of the Effects of Provider Reimbursement Mechanisms and Managed Care on the Use of Antimicrobial Drugs in the NIS and Developing Countries

Implementing Organization: RPM/MSH

Description: A comprehensive and systematic review of published and unpublished studies on the impact of managed care and provider reimbursement mechanisms on the use of antimicrobial drugs in developing countries will be undertaken. An analytical framework will be developed to provide a structure for evaluating the impact of the above reforms (interventions) on the behavior of providers and consumers in use of antimicrobial drugs. This review will build on the experience of other efforts to identify studies that assess the impact of interventions on drug use in general and antimicrobial use in particular. Previous approaches started from a general drug use perspective. This review proposes to identify relevant studies searching for studies on the impact of managed care and provider reimbursement mechanisms.

On-line search engines, and databases such as the INRUD Bibliography and the Cochrane Library will be used to identify relevant published studies and overviews. In addition, World Bank task managers and USAID contractors that work on health reform in the NIS and developing countries will be contacted to identify unpublished studies. Studies that will be included in the review will have the following characteristics:

- Studies that focus on the use of antimicrobial drugs;
- Studies that examine the impact of one or more of following interventions: managed care, provider payment mechanisms;
- Studies that include an assessment of the impact of the intervention on the use of antimicrobial drugs;
- Studies of these interventions in developing countries and the NIS.

Because it is anticipated that few rigorous studies will be identified, this review will also search for systematic overviews and relevant primary reports on the impact of managed care and provider reimbursement mechanisms on drug utilization in general and antimicrobials in particular, in North America and Western Europe. This study will then attempt to identify lessons learned from developed country experiences that should be considered in he potential implementation of such approaches in developing countries and the NIS.

Countries/Regions: Studies in Africa, Asia, Latin America and the NIS.

1.10: Technical Paper on Fixed-Dose-Combination (FDC) Drug Products

Implementing Organization: RPM/USP

Description: Fixed-dose combination (FDC) drug products are widely produced and marketed throughout the world. Such products represent a relatively simple way a drug manufacturer can extend its product lines (and profits) at a minimal cost. Although most FDCs would be considered as irrational therapy, there is some support for their use in cases where multiple-drug regimens can be reasonably standardized and compliance to therapy is absolutely essential. There is a considerable body of knowledge relating to FDCs. In addition, because of their widespread registration and availability, there is considerable experience with their use in patient care (either by a care-giver or through self-care).

This activity would focus on collecting available FDC information and experiences (by literature and policy review and through interviews with key individuals who are knowledgeable about FDCs), analyzing the issues presented, identifying the pertinent areas of concern, and subjecting the draft report to the scrutiny of experts and other interested parties. As part of the information/experience collection, selected FDCs on the market will be used as case studies/examples; policies of regulatory agencies and manufacturers will be explored; and research relating to the effect of FDCs on patient compliance/adherence will be reviewed. A group of experts will be asked to serve as a reviewing body, with opportunity for public review and comment. The process will be open and transparent. Most of the discussions will make place via mail, telephone, and e-mail, with one face-to-face meeting of the individuals serving on the reviewing body scheduled towards the end of the deliberation period. The final draft document will be published for the review and comment of all interested parties.

Countries/Regions: Not applicable.

AMR Component 2: Improving the Understanding of Antimicrobial Resistance

2.1 Determining the Relative Importance of Various Factors in the Development of Antimicrobial Resistance

Implementing Organization: JHU/FHACS

Description: We propose to develop a model, using data collected in one developing country, that examines the relative importance of a population's various exposures to antibiotics, and the interrelationship between the exposures, to the population's carriage rate of drug-resistant bacteria; and to then test the predictive strength of the model in a second country.

In several communities in each country, data relevant to all possible antibiotic exposures of a large magnitude will be collected through site-appropriate methods, including surveys, observation, and examination of records at farms, public health facilities, private physicians' offices, pharmacies and

households. Antibiotic resistance carriage rates will be determined by sampling and testing nasopharyngeal and enteric organisms from children at a variety of sites in each community. Using data from the first country, regression models will be developed to examine the strength of and interrelationship among various types of antibiotic exposures, including for example, possible additive or multiplicative effects among the exposures, in determining a community's rate of antibiotic resistance. Data from the second country will be used to test and refine the model.

Countries/Regions: The study will be conducted in two developing countries which have yet to be determined. It would be useful to develop the model in countries with many different types of antibiotic exposures as well as exposures that are highly variable between areas within each country. This would allow us to examine the influence of several antibiotic sources on the development of antimicrobial resistance. Including sites with different disease profiles, for example one country with malaria and one without, would permit examining the influence of divergent disease settings on the model's operation. Possible countries might include Egypt, Zimbabwe, South Africa, Bangladesh, Indonesia, and the Philippines.

2.2 Mathematical Modeling of Antimicrobial Resistance Emergence and Spread

Implementing Organization: WHO/CDS

Description: These activities will be undertaken in partnership with the Wellcome Trust Epidemiology Research Centre, University of Oxford, UK.

1. Definition of data sets available to WHO and those required for particular models of human-to-human spread and animal-to-human transfer of resistant strains and resistance genes.
2. Selection of one or two scenarios for which sufficient data exist for construction of models.
3. Establishment of mathematical models for one or two scenarios (depending on data availability and complexity).
4. Examination of effect of resistance containment interventions on the model.
5. Design and execution of a field study to test the interventions which are predicted from the model to be effective. (Further funding will be required for this activity.)

Countries/Regions: To be determined.

2.3 Non-medical Uses of Antimicrobials and the Impact on Human Health

Implementing Organization: WHO/CDS

Description:

1. Meetings of a collaborative working group between WHO and key partners to advocate for operational research and data gathering to fill identified gaps, including strengthening of surveillance of antimicrobial resistance in bacteria from food of animal origin;
2. Definition of collaborative activities with industry working group (established with IFPMA and COMISA);
3. Preparation and dissemination of reports.

Countries/Regions: Not applicable.

2.4 Measuring, Understanding and Changing Irrational Drug Use

Implementing Organization: WHO/HTP/EDM

Description: The draft manual of non-quantitative indicators will be field tested in four countries. These tests would be conducted in close collaboration with INRUD/MSH. The final version of the manual would be disseminated to national essential drug programmes, researchers and trainers in rational drug use and relevant non-governmental organizations.

Countries/Regions: Potential field test sites include Benin, Indonesia, Kenya, Philippines, South Africa, Uganda, and Zambia.

2.5 Indicators for Measuring Antimicrobial Use in Hospitals

Implementing Organization: RPM/MSH

Description: Tasks include a focused literature review and survey of key researchers and INRUD members. RPM intends to produce a draft instruction manual that would include the rationale, definition, and calculation for proposed indicators, model data collection forms and proposed methods, and techniques to collect data needed to derive the indicators. Key members of the INRUD Network, WHO DAP, USP advisory panels (Drug Utilization Review and International Health), and leading drug use intervention researchers will be invited to review the proposed methodology and indicators.

RPM will conduct a field test of these indicators, data collection forms and data collection methods and techniques. It is expected that members of the INRUD network will collaborate in the field test. Results of the field test will be reviewed at a post-field test workshop and the indicators and instruction manual revised accordingly.

Once the manual is revised, its availability will be announced in electronic and print fora (E-drug, INRUD News, Essential Drug Monitor). It will be determined later if it may be appropriate to publish the manual in collaboration with WHO. Field test results may be published in the INRUD News, Essential Drugs Monitor and a peer-reviewed journal. The methodology will be incorporated in the INRUD-WHO Promoting Rational Drug Use and the MSH Managing Drug Supply courses.

Countries/Regions: Field tests in Africa, Asia, and potentially Latin America

2.6 Evaluation of the Impact of IMCI Case Management Approach on Antimicrobial Use Practices and Drug Resistance

Implementing Organization: CDC/NCID

Description: Before implementation of case management, baseline data will be collected including rates of antibiotic prescribing and use among children; respiratory tract carriage rates for resistant *S. pneumoniae* and *H. influenzae*; and, if possible, carriage rates for resistant fecal flora. Local investigators will be trained in study methods including epidemiological survey techniques and laboratory methods for isolation, identification, and susceptibility testing of respiratory tract and enteric pathogens. Susceptibility test results from these baseline investigations will inform the selection of appropriate antibiotic therapy for

case management guidelines. During case management training, the risk of antibiotic resistance and the importance of strict adherence to prescribing guidelines will be emphasized. After one year of case management implementation (and potentially at intervals thereafter), rates of antibiotic prescribing, use, and resistance will be assessed among patients managed by IMCI-trained providers and compared with rates among patients of untrained providers.

Countries/Regions: Areas that are in the process of implementing IMCI would be appropriate for this activity. This includes sites in Central Asia (Kazakhstan), Bangladesh (in conjunction with ICDDR,B), and several sites in Africa or Latin America. We will work with international partners to identify the best site for this activity.

2.7 Improving the Treatment of Bacterial Meningitis in Developing Countries

Implementing Organization: WHO/CAH

Description:
1. Designing and implementing a multi-country study to strengthen facilities for CSF; culture and basic susceptibility testing to examine the prevalence of *S. pneumoniae*, *H. influenzae,* and *N. meningitidis*;
2. Developing facilities for CSF cultures and basic susceptibility testing where they are not available;
3. Developing drug-switch guidelines based on antimicrobial resistance data.

Country(s)/Region: The study will be conducted in Africa, Asia, and Latin America. Discussions are underway with interested researchers.

2.8 Relationship between in vitro Antimicrobial Resistance of *S. pneumoniae* and *H. influenzae* Blood Isolates and in vivo Response to Penicillin in Severe Pneumonia

Implementing Organization: WHO/CAH

Description:
1. A proposal development workshop to be held to develop a protocol to study this question.
2. In a multi-centre (18 hospitals in five countries) observational study of hospitalized children with severe pneumonia on injectable penicillin treatment will be observed.
3. Blood cultures will be obtained in all patients to identify and document the resistance patterns of *S. pneumoniae*.

Country(s)/Regions:
Argentina: Hospital Pedro de Elizalde Buenos Aires, Hospital Durand Buenos Aires, Hospital Sor Ludovica La Plata, Hospital Notti Mendoza; *Brazil:* Hospital das Clínicas/UFMG, Belo Horizonte, Instituto Materno Infantil, Recife, Inst Ped. Pueri. M. Gesteira, Rio de Janeiro, Hospital Universitário, Salvador, Hospital Aliança, Salvador, Hospital Santa Casa, São Paulo, Hospital Darci Vargas, São Paulo; *Columbia:* Hospital La Misericordia Bogotá, Clínica Colsubsidio Bogotá, Hospital Universitário Cali, Hospital San Vicente de Paúl Medellin; *Peru*: Instituto de Salud del Niño; *Dominican Republic:* Hospital Robert R. Cabral Santo Domingo, Hospital de Los Mina Santo Domingo.

2.9 Investigation of the Impact of Antimicrobial Agent, Dose, and Treatment Duration on Carriage of Resistant Respiratory Tract Pathogens

Implementing Organization: CDC/NCID

Description: Two approaches will be pursued to address this objective: 1) Children will be randomized to receive routine or high dose therapy with cotrimoxazole or amoxicillin with impact on NP respiratory tract pathogens being assessed by culture before and after therapy. Compliance will be evaluated by history and pill count and these data will be incorporated along with drug and dose in a multivariate model with resistant carriage as an outcome. 2) Children will be enrolled from pharmacies in the community when their parent purchases cotrimoxazole or amoxicillin at inadequate dose or duration (≤3 days therapy). Impact on resistant carriage will be assessed by NP culture before and after therapy. Analysis will compare baseline and follow up results as well as comparing the impact of the routine 5 day therapy with the shorter

Countries/Regions: Dominican Republic.

2.10 Impact of Fansidar Use on Cotrimoxazole Resistance

Implementing Organization: CDC/NCID

Description: Two approaches could be taken in this investigation; which is optimal would depend on the specific characteristics of the study area. The first approach is to identify two malaria endemic areas: one where chloroquine remains the recommended therapy for malaria and another where fansidar is being introduced as therapy. In the fansidar use area, NP carriage of cotrimoxazole resistant respiratory tract pathogens will be assessed before and after therapy for children who receive fansidar versus those who receive no antimicrobial. In addition, longitudinal NP swab surveillance, according to guidelines developed in the above surveillance proposal, will be conducted in the fansidar and the control areas to determine whether trends in cotrimoxazole resistance differ between the two areas, controlling for cotrimoxazole use in each area. A second approach would be to perform cross sectional surveys in areas with different rates of malaria (e.g., holoendemic, seasonal, and no malaria) and compare rates of cotrimoxazole resistance controlling for differences in cotrimoxazole use.

Countries/Regions: The most likely site for this study is Sub-Saharan Africa where fansidar is being introduced in many areas due to the prevalence of chloroquine resistance. CDC has previous experience and study sites in Malawi and in Kenya that may be appropriate for this study

2.11 Advocacy and Information to Combat Antimicrobial Resistance

Implementing Organization: WHO/HTP/EDM

Description: WHO/HTP/EDM will develop and disseminate a theme issue of The Essential Drugs Monitor devoted to antimicrobial. WHO/HTP/EDM will select, commission, review, adapt, reject or accept material in the normal way, with full editorial control. The outcome of the November 1998 WHO meeting on the Global Strategy for the Containment of Antimicrobial Resistance will be covered. Clear terms of reference including time frames would be agreed with contributors. The issue will be translated and published in the usual four languages. Expanded distribution would be pursued through the

WHO/HTP/EDM and WHO/CDS networks in addition to the WHO Regional Offices. The print run would be increased according to need.

Countries/Regions: 160 countries

2.12 Training on the Rational Use of Drugs for Pharmacy Undergraduates

Implementing Organization: WHO/HTP

Description: Regional workshops with heads of pharmacy schools in Asia, Latin America and Francophone Africa; development of a document with core curriculum and practical recommendations how to review/adapt any existing curriculum; field testing of the document; production of a WHO core curriculum with relevant training materials. This is a project which will require 2-3 years to complete.

Countries/Regions: Not applicable.

2.13 AMR 'Toolkit' for Information and Education

Implementing Organization: WHO/CDS

Description: Communication with international partners to identify existing materials; preparation of appropriate new materials; collaboration with external technical expert to develop video and CD-ROM and to package toolkit.

Countries/Regions: Not applicable.

2.14 Evaluation of the Impact of Repeated Mass Azithromycin Prophylaxis on Antimicrobial Resistance in Countries Initiating Trachoma Control

Implementing Organization: CDC/NCID

Description: A single, well-defined village or region will be used as a case study for the impact of mass azithromycin prophylaxis. An appropriate village/region that is not undergoing mass chemoprophylaxis will be selected to serve as a control population. In the village undergoing chemoprophylaxis, we will swab the nasopharynx of each child <6 years of age before they receive azithromycin to determine the baseline carriage rate of antimicrobial resistant *S. pneumoniae* and *Haemophilus influenzae*. Depending on the size of the village, a follow up swab survey on all children or a subset of children will be conducted one month later and then at six month periods. Additionally, before the first mass chemoprophylaxis treatment, we will establish surveillance at the central hospital and outpatient clinic in the village for invasive pneumococcal disease, pharyngitis, skin infections, *Chlamydia trachomatis* infections (STD and trachoma), and if possible, acute rheumatic fever and low-birth weight infants. Similar surveillance will be established in the control village, and swab surveys will be conducted at the same time points as in the village receiving chemoprophylaxis.

Countries/Regions: Egypt and Nepal.

AMR Component 3: Developing Methods to Detect Resistance

3.1 Comprehensive Laboratory Manual for Isolation, Identification, and Susceptibility Testing of Common Outpatient Pathogens

Implementing Organization: CDC/NCID

Description: CDC, in conjunction with WHO, has developed separate laboratory manuals that address one or more of isolation, identification, and susceptibility testing for the pathogens listed above. These manuals have been published separately and are not all currently available or up to date. In addition, susceptibility testing methods are not included in all manuals and the methods that are included do not include the E-test which recently has been shown to be useful for testing susceptibilities in a developing country setting. Under this project, CDC microbiologists will make necessary revisions and additions to the current manuals and integrate these components into a single manual with a common format for each of the pathogens. The manual will be field tested with a CDC microbiologist providing training in a developing country setting. Based on results of this evaluation, any needed changes will be made. As a follow-on activity, we will translate the manual and collaborate with other international organizations to disseminate it and provide training or consultation.

Countries/Regions: The field test will take place in two countries in Africa, Asia, or Latin America where ongoing surveillance for antimicrobial resistance is planned. The site will be selected with input from USAID & WHO.

3.2 Standardized Sampling Methods for Assessment of *H. influenzae* and *S. pneumoniae* Antimicrobial Resistance

Implementing Organization: JHU/FHACS

Description: We will evaluate several industrial sampling methods as candidates for a standardized sampling method to determine the prevalence of antimicrobial resistant *Haemophilus influenzae* and *Streptococcus pneumoniae* in different populations including asymptomatic children in the general community, outpatients and hospitalized patients. We will evaluate nasopharyngeal cultures in all populations and evaluate isolates from normally sterile sites (blood, cerebrospinal fluid, pleural and joint fluid from sick outpatients and hospitalized patients.

Data from laboratory records from studies that have already been completed will be reviewed to develop models that can be used to compare different sampling industrial sampling methods.

The simplest approach would be a plan with a fixed *n* determined on the basis of the magnitude of change that is to be detected and the risk of failing to detect the change. If the sample is to be taken from several populations (hospitals), a somewhat more complex design would be needed as an adaptation of the EPI approach to account for the "design" effect.

Depending upon the specific situation, four industrial sampling designs might be considered. The first is a double sampling method that starts with a small n to determine whether conditions are clearly so "good" or "bad" that a decision can be made on the basis of limited evidence. If conditions are in the "gray" area,

a second sample is taken, and the decision is based upon the aggregate information.

Sequential sampling represents a further refinement of this technique. In that case certain formulas are applied to establish bounds of experience. Every child would be tested and results plotted in chronological order, until the chart takes you above or below the two boundary lines. At that point it is possible to stop sampling and make a definitive judgment. Obviously, this needs to be explained by means of a diagram. The point, however, is that you continue sampling only until the precise moment when you have enough information to draw appropriate conclusions.

Another method calls for the sampling of every *kth* product (child) until trouble is found. Thereafter, every child would be tested until the trouble is corrected. I am not sure that your situation is such that "trouble" arises and is corrected, so that you can return to "normal" surveillance, but some modification of this approach might be relevant.

Finally, there is the normal-tightened-reduced sampling procedure. This begins with a designated "normal" sample size and criteria for decision making. If conditions are found to be "suspect" according to predetermined rules, a more stringent sample design is introduced. In contrast, if a predetermined period of time without difficulty elapses, a reduced, less costly sampling procedure is triggered.

In the second year of the project, sampling methodologies will be field tested in several developing country settings. Optimal culture methods will be used including selective media if appropriate in the surveys.

Countries/Regions: Data from sentinel surveillance performed in Guatemala, India, an African country and the United States will be reviewed. On site studies in Guatemala, India and an African country will be conducted in year 2.

3.3 Evaluation of Nasopharyngeal Swab Surveillance for Antimicrobial Resistance Among Respiratory Tract Pathogens

Implementing Organization: CDC/NCID

Description: We will meet with investigators from sites where surveillance has been conducted using NP isolates and with other experts to: 1) summarize the results of these investigations based on published and unpublished data supplied by the investigators; 2) assess the impact of different approaches to enrollment and varying durations of surveillance on results of the studies; and 3) develop a consensus regarding optimal surveillance methodology.

Countries/Regions: Not applicable.

3.4 Detection of Antimicrobial Resistance *in vivo*

Implementing Organization: WHO/CDS

Description: Establishment (in collaboration with the WHO Office of HIV/AIDS and Sexually Transmitted Diseases, AD) of study design, based on lot quality assurance, to detect gonorrhoea resistant to antimicrobial treatment. Critical review of study design with experts in the WHO Gonococcal

Antimicrobial Surveillance Programme (GASP). Field test in parallel with laboratory tests to detect resistance in vitro. Laboratory tests will be carried out in one or more of the laboratories participating in GASP and will provide the opportunity for strengthening techniques in these laboratories.

Countries/Region(s): The field study will be carried out in southern Africa in partnership with the South African Institute for Medical Research, Johannesburg, South Africa.

3.5 Using Clinical Treatment Failures to Monitor Antimicrobial Resistance

Implementing Organization: WHO/CAH

Description:

1. A study, conducted in the community as well as in the hospital, will determine the relationship between treatment failures assessed clinically and prevalence of antimicrobial resistance to the first line antimicrobial determined on nasopharyngeal swab isolates of *S. pneumoniae* and *H. influenzae*.
2. A detailed history of prior antimicrobial use will be obtained at the beginning of therapy with special reference to the antimicrobial recommended by WHO ARI standard case management guidelines e.g. cotrimoxazole, amoxicillin, chloramphenicol etc.

Country(s)/Regions: The study will be conducted in Asia. Discussions are underway with interested researchers.

3.6 Magnitude and Trends of Resistance in Priority Infectious Diseases

Implementing Organization: WHO/CDS

Description:

1. Expand and continue to implement projects for monitoring MDR-TB in high priority countries;
2. Prepare and evaluate DRS protocols following standardised methodological guidelines. This will include technical advice, site visits and quality assessment;
3. Organise a meeting to review the data collected through monitoring of drug-resistant malaria by determining therapeutic efficacy of anti-malarial drugs;
4. Strengthen monitoring of gonococcal resistance and improve the epidemiological basis of the data collection;
5. Provide guidelines and training to enable the building/strengthening of networks to monitor other priority bacterial infections;
6. Maintain and expand as required networks of reference laboratories for quality assurance of antimicrobial susceptibility testing (incl. MDR-TB and DR-malaria)

Countries/Regions: To be determined.

AMR Component 4: Responding to Data on Antimicrobial Resistance and Drug Use

4.1 Model Prescribing Information -- Drugs Used in Bacterial Infections

Implementing Organization: WHO/HTP/EDM

Description: The first draft of this manual is almost completed. It now needs to be reviewed and edited by an infectious disease specialist before being subjected to a broad consultative procedure including review by the relevant technical divisions within WHO, national Drug Regulatory Authorities, scientists, relevant non-governmental organizations including the International Society of Chemotherapy, International Union of Pharmacology and the International Federation of Pharmaceutical Manufacturers Associations. Relevant parts of the manual on establishing a national programme on promotion of rational drug use and antimicrobials in particular (see activity 4.3: "Guidelines for Establishing a National Programme....") will be included and frequent cross referencing made.

Dissemination of the manual to all national regulatory authorities and the relevant non-governmental organizations is routine. Additional dissemination will be undertaken as appropriate by EDM and CDS.

Country/Regions: The six Regional Offices of WHO will be involved in the consultative procedure.

4.2 Guidelines for National Policy Makers and Health Administrators on the Containment of Antimicrobial Resistance (linked to activity 5.1)

Implementing Organization: WHO/HTP/EDM

Description: A skeleton outline has been prepared. This will be developed in consultation with all relevant technical divisions within WHO, national drug regulatory authorities, scientists, relevant non-governmental organizations, including the International Society of Chemotherapy, International Union of Pharmacology, the International Federation of Pharmaceutical Manufacturers Associations and the Consumers Union, and relevant professional associations.

Dissemination of the manual to all national regulatory authorities and the relevant non-governmental organizations is routine. Additional dissemination will be undertaken as appropriate by EDM and CDS.

Country/Regions: The six Regional Offices of WHO will be involved in the consultative procedure and a meeting to discuss the draft document.

4.3 Guidelines for Establishing a National Programme to Promote Rational Drug Use, and Rational Use of Antimicrobials in Particular (linked to activity 5.1)

Implementing Organization: WHO/HTP/EDM

Description: Commission an analysis of current evidence based interventions available to promote rational use of drugs (special emphasis on cost effectiveness and antimicrobials). The draft report of this analysis will be used as the basis for a review by a global panel of experts on implementation of such

interventions at national level. The draft document produced will be field-tested before finalization. Activities will be undertaken with INRUD and the School of Public Health in Boston, and other experts as needed. Relevant parts of the national guidelines on containing antimicrobial resistance (see activity 4.1: "Model Prescribing Information -- Drugs Used in Bacterial Infections") will be included in this manual and frequent cross referencing made. The final document would be complementary to that proposed in activity 4.1. The final version of the manual would be disseminated to ministries of health, national regulatory authorities, essential drug programmes, researchers and trainers in rational drug use as well as appropriate relevant non-governmental organizations by EDM and CDS.

Country/Regions: WHO/HTP/EDM in Geneva

4.4 Guidelines for Containing Antimicrobial Resistance at Hospital Level ("Hospital Package")

Implementing Organization: WHO/HTP/EDM; WHO/CDS

Description:
1. Review of available guidelines on establishment and function of HDTCs and ICCs;
2. Modification of guidelines if required for developing country conditions;
3. Development of draft text on RDU (see Review, AMR Component 1) and infection control to be incorporated into guidelines;
4. Pilot in at least two developing countries and evaluate changes in actual prescribing of antimicrobials;
5. Review text with global consultation;
6. Issue document and disseminate through Ministries of Health and university teaching hospitals, essential drug projects, RUD projects, and appropriate non-governmental agencies.

Country/Regions: Zimbabwe.

AMR Component 5: Preventing and Slowing the Spread of Antimicrobial Resistance

5.1 Integrated Country Programmes for Containment of Antimicrobial Resistance ("Country Intervention Package")

Implementing Organization: WHO/CAH; WHO/CDS; WHO/HTP/EDM

Description: The package will contain a series of activities to be initiated, together with indicators of efficiency and benefit, in the selected countries.

1.Situation analysis: Surveillance studies to determine the prevalence of priority infectious diseases, prevailing antimicrobial resistance patterns and knowledge of antimicrobial use. (Disease surveillance will be coordinated with other Divisions in WHO).

2.Activities in laboratory-based surveillance:

2.1. Provision of laboratory-based training in microbiological diagnosis and detection of resistance and analysis of resistance data, and laboratory capacity strengthening;

2.2.Training trainers in order to enable sustainable in-country technical training in lab-based resistance

detection;

2.3. Assistance to countries to establish external quality assurance schemes for antimicrobial susceptibility tests;

2.4. Assistance in initiating a national surveillance network.

3. Activities in education and training:

3.1. Development of continuing education programmes for laboratory technologists, prescribers and other healthcare professionals;

3.2. Public education programmes;

3.3. Development of training modules for health workers in the use of assessment and treatment algorithms, such as the ones developed and used in the IMCI;

3.4. Development of a core undergraduate medical and pharmacy curriculum for training in the rational use of drugs particularly antimicrobials.

4. Activities in guidelines and policy formulation:

4.1. Organization of workshops to bring together policy-makers, physicians, pharmacists, laboratory staff, nurses and community health workers to review national antimicrobial resistance data and current antimicrobial use practices, to identify constraints in information flow and to develop national plans of action for the surveillance and containment of resistance;

4.2. Assistance in development of national antimicrobial use guidelines and drug use indicators relevant for antimicrobial use. These activities will, as far as possible, be integrated within the scope of a national policy to promote rational drug use.

Countries/Regions: Three pilot developing/transition countries will be identified by WHO. Criteria for inclusion to be considered will include: (1) existence of national drug policy; (2) existence of an essential drug programme with a rational use of drugs component; (3) existence of suitable microbiology laboratory facilities; (4) existence or experience of WHO projects including IMCI; (5) political willingness to be involved in a project.

5.2 APUA Chapter Development

Implementing Organization: Alliance for the Prudent Use of Antibiotics

Description:

A. Development of new chapters

- Identification of qualified leaders in appropriate professional societies and government and non government organizations through APUA scientific advisory board contacts;
- Preparation of introductory packets;
- Initial telephone contacts and mailings of APUA chapter information and background packet to 100-200 potential members;
- Explaining of chapter guidelines and agreement;
- Gain agreement on contract and chapter representation;
- Organize initial meeting of chapter;
- Identification of office support needs;
- Establish initial link with other chapters;
- Mailing of APUA newsletters;
- Assist with outline of goals and objectives.

B. Support of established chapters

- Identify local office support needs and provide assistance;
- Assist with development of local work plans and priority objectives and activities reflecting

both local needs and relating to the global planning effort;
- Establish electronic and other links with other chapters and the larger scientific community dealing with antibiotic resistance;
- Annual chapter surveys : Develop, conduct and compile and disseminate results;
- Organize local workshops regarding antibiotic research and education;
- Disseminate educational and membership materials: newsletter, video, relevant publications and materials to key authorities, professional groups;
- Compile and disseminate standards and guidelines on antibiotic resistance surveillance and antibiotic use;
- Send experts to country to advise on research and training needs;
- Development of guidelines for review of chapter small grants proposals;
- Provide small grants for local research, surveillance and educational programs;
- Translate and distribute APUA educational materials into the native language;
- Encourage and edit original research from chapters for inclusion in the APUA news;
- Publish and disseminate APUA newsletter to chapter members and relevant contacts;
- Collect and disseminate chapter success stories;
- Assist with development of local guidelines for surveillance and antibiotic use;
- Conduct mentoring and international networking and exchange programs;
- Develop model training sessions;
- Development of press packages.

Countries/Regions: Argentina, Columbia, Dominican Republic, Venezuela, and other countries in Latin America.

5.3 AM Booklet for Pharmacists and Drug Sellers

Implementing Organization: RPM/USP

Description: Using Nepal ID funding, USP will research the antimicrobial drug knowledge and consumer counseling practices of drug sellers in Nepal in cooperation with the NCDA. Emphasis will be placed on antimicrobials used to treat high priority diseases such as pneumonia, Shigella and sexually transmitted infections. A template for a booklet for pharmacists and drug sellers (which can be adapted by other countries) will be completed using the Nepal research results and USP's patient information database, appropriately adapted for Nepal. In addition, information relating to appropriate counseling techniques will be included based on USP's patient counseling guidelines, again, adapted for Nepal. Nepal ID funds will allow the booklet to be tested in Nepal. Core funds will be used to develop the template, disseminate the booklet outside of Nepal as a model and to assist other countries with adapting/translating the model for local use through a sub-agreement mechanism. Core funds will also be used to develop a facilitator's guide for use by trainers of retailer-groups.

Countries/Regions: Nepal

5.4 Training Modules for Drug & Therapeutics Committees and Antibiotics Sub-Committees

Implementing Organization: RPM/MSH

Description: The materials will include, minimally, sessions on (1) the role and functions of a DTC, (2) criteria for antimicrobial drug selection, (3) economic analyses for antimicrobial drug selection, (4) the appropriate use of in vitro antimicrobial susceptibility testing, (5) how to evaluate the clinical literature on drug efficacy and safety, (6) how to conduct analyses to target drug use interventions, (7) a framework to improve the use of antimicrobial drugs, (8) effective strategies to improve antimicrobial drug use, (9) sources of reliable information on antimicrobial drugs, and (10) effective communication skills and team work.

Tasks include a review of relevant literature and a selective survey of these committees to gather information to design the training modules. RPM intends to prepare (1) a discussion paper on the role of these committees and the need for skills development in developing countries and (2) a draft outline of modules, stating the rationale, objectives, key content, and a preliminary list of suggested readings for each module, that will be reviewed before actual drafting of modules. Once the modules are drafted, an alpha course will be organized and conducted in collaboration with interested partners.

Once the alpha course has conducted, availability of materials will be announced in electronic and print fora (E-drug, INRUD News, Essential Drug Monitor). Field test results may be published in the INRUD News, Essential Drugs Monitor and a peer-reviewed journal. Subsequent course may be organized through INRUD, WHO, or other interested organizations for regional or national level training of trainers.

Countries/Regions: Africa or Asia (to be determined)

5.5 Improving the Use of Antimicrobials through Interventions Aimed at Health Professionals, Drug Sellers and Community Health Workers

Implementing Organizations: HIID/ARCH and RPM/MSH

Description: The proposed drug use research portfolio includes several studies proposing innovative approaches to behavior change, including group interactions with drug sellers involving community members, or the use of local hospital specialists as educational leaders to facilitate change among primary health care physicians.

In addition, a number of studies target the use of antibiotics in hospitals. Their focus ranges from teaching hospitals to district hospitals; public to private to mission institutions; neonatal intensive care units to pediatric outpatient departments; specialists to general medical officers. A number of studies focus on improving and expanding the role of Pharmacy and Therapeutics Committees, the mainstay in many developed countries of efforts to improve the quality of prescribing.

The top-ranked research pre-proposals which address antimicrobial drug use were submitted by investigators in Asia and Africa include:

- *Indonesia*: Reducing the use of expensive antibiotics for ARI in children utilizing a face to face intervention facilitated by hospital P&T committees at health center level to improve compliance to standard treatment guidelines for ARI
- *Indonesia*: Small group discussion among paramedics at health centre level to improve compliance to

acute respiratory infection standard treatment guidelines
- *Nepal*: Test of strategies for implementing STS in improving use of drugs.
- *Philippines*: Improving antibiotic usage in the Philippines through interactive patient-oriented and administrative practices
- *Philippines*: The effect of interactive group discussions with mothers and a regulatory officer on dispensing practices of drug store clerks
- *Philippines*: The effect of an educational activity on the drug purchasing practices of municipal mayors and village heads
- *Thailand*: Improving clinical and economic rationality of antibiotic prescribing in a teaching hospital
- *Thailand*: Factors responsible for the success of hospital P&T committees in improving use of antimicrobial agents for surgical prophylaxis and lower respiratory infections in provincial hospitals
- *Ghana*: Improving doctors´prescribing habits at a teaching hospital
- *Kenya*: Influencing prescribing behavior: the use of drug audit as an intervention tool
- *Kenya*: Effect on treatment of ARI cases after introducing clinical guidelines and P&T committees in mission health facilities
- *South Africa*: The impact of an antimicrobial policy on the use of antimicrobials at Ga-Rankuwa Hospital
- *Uganda*: Drug utilization review program targeting private pharmacists and drug retailers in Uganda.
- *Uganda*: The impact of decentralization on access to health services, use and availability of drugs in two district hospitals in Uganda
- *Vietnam*: Improving community drug use through peer review and implementation of clinical guidelines.

Each partner of the Joint Initiative on Drug Use Intervention Research plans to contribute with technical assistance through structured proposal development and data analysis workshops and on-going technical support to implement selected studies, funding for participants to attend the workshops, and funding of selected studies. The first proposal development workshop was hosted by the WHO Collaborating Centre for Clinical Pharmacology and Drug Policy Studies in Indonesia, secretariat for the Indonesia INRUD Country Core Group, in May 1998. The second proposal development workshop will be held in Uganda in September 1998. ARCH and RPM intend to provide continuing technical support to selected researchers who will carry out the study protocols developed at these workshops. RPM proposes to provide financial support for one intervention study, and ARCH will support as many as feasible, depending on estimated costs and level of funding available. A Data Analysis workshop is proposed for late 1999 in Asia for the teams who participated in the Proposal Development Workshop that was held in Indonesia this past May.

Countries/Region: Asia and Africa (see Description for countries)

5.6 Promoting Rational Use of Antimicrobials in the Private Sector

Implementing Organization: WHO/HTP/EDM

Description:
- Assist 3 developing countries in developing a national strategy and action plan to promote rational use of antimicrobial drugs in the private sector to include: (1) strengthening regulatory control over sales and drug promotion; (2) working with professional associations to encourage rational use of antimicrobials; (3) working with consumer groups active in the wider community; and (4) working with industry associations on development and enforcement of self-regulatory codes.
- Based on the experience in these countries prepare a draft manual with guidelines on developing and implementing such a plan.
- Production and dissemination of the guideline to all national regulatory authorities, ministries of health

and the relevant non-governmental organizations. Additional dissemination will be undertaken as appropriate by WHO (DAP, DMP and EMC).

Countries/Regions: Philippines.

5.7 Development of an Intervention to Improve Compliance with Antimicrobial Therapy using IMCI Drug Counseling Guidelines

Implementing Organization: JHU/FHACS

Description:
***Phase 1* (3 months)** Data collected in this phase will be used to design locally-appropriate instruments for subsequent phases.

Semi-structured interviews with service providers and officials. To examine institutional factors that facilitate or obstruct adherence to treatment recommendations, a series of 15 interviews will be conducted with officials of the IMCI program of the Ministry of Health, district health officials and health facility personnel at the hospital, dispensary and health post level. The interviews will cover obstacles encountered in implementing the IMCI approach in Uganda, factors limiting adherence to treatment recommendations, suggestions (methods or specific questions) for data collection on treatment-seeking, and perceptions of the antimicrobial resistance problem in Uganda.

Semi-structured interviews on knowledge and perceptions of medications. A sample of 30 parents of young children will be administered a 30 minute semi-structured interview on knowledge and perceptions of medications. Topics will include free-listing of types of medications, pile sorting (classification) of locally-available medications for children, and local names for medications.

Direct observation of provider-patient interaction. Activity in the waiting room and patient-provider interaction in health facilities will be directly observed in facilities which have and have not implemented the IMCI approach. Approximately 2 days of observation will be conducted in each facility selected.

Exit interviews Exit interviews will be conducted with parents of young children upon leaving the health facility. Respondents will be administered a brief survey about how long they waited, what happened in the appointment, what treatment they were told to take, etc., in order to assess the degree to which people understand the information they are being given.

***Phase 2* (3 months)**
Evaluation of compliance with treatment recommendations In the districts chosen for the study, lists of facilities that are performing "gold standard" IMCI [applying the 3 components of treatment counseling; explain, demonstrate, verify comprehension] and of facilities that have not yet implemented IMCI will be compiled. Children receiving outpatient care at the two types of facilities will randomly be selected for follow-up. The IMCI clinical classification of all children will be determined by trained observers. Children selected for follow-up will be <5 years of age and have a clinical diagnosis of pneumonia, malaria, dysentery or acute ear infection. Children will receive the nationally recommended first-line antimicrobial agent for their clinical diagnosis. All children will be followed-up in the home after 5 days. The two groups will be compared on compliance with treatment. Serum samples may be collected on a sub-sample of children to correlate compliance histories with serum levels of antimicrobials. Qualitative and quantitative data will be collected from compliers and non-compliers with antimicrobial therapy. Areas of

particular interest will include the formulation of the medicines, the type of illness, perceived severity of illness, perceived quality of the counseling received, and the role of other family members on treatment practices. It is unlikely that the mortality outcome for the two groups will be able to be compared due to the large sample sizes that would be needed. Barriers to compliance with a full course of antimicrobials will be identified.

***Phase 3* (3 months)**

Intervention development. Data from the second phase will be analyzed. Data on barriers to antimicrobial compliance will be used to develop an intervention or interventions that can be implemented at the time of the facility visit. These interventions will be developed with local health staff and program managers. An emphasis will be placed on developing interventions that are feasible using local resources, acceptable to local staff and communities, and time efficient. Potential interventions will be pre-tested.

***Phase 4* (3 months)**

A design similar to Phase 2 will be implemented. Facilities already implementing "gold standard" IMCI counseling will be randomized to continue with existing counseling, or to implement an improved counseling approach based on the results of the preceding phases. A costing element will be added to estimate the cost of adding the intervention (s) to routine outpatient practice. All children will be followed up in the home at 5 days and compliance with treatment will be assessed. The same variables will be evaluated. Qualitative and quantitative methods will again be used to assess compliers and non-compliers. The effectiveness and cost-effectiveness of the intervention (s) to improve antimicrobial compliance will be determined.

Countries/Regions: The Africa region is proposed for this study. Uganda is proposed as the likely site for the following reasons: 1) High morbidity and mortality amongst children <5 from lower respiratory tract infections and malaria; 2) Commitment by the ministry of health to use IMCI as its primary child health strategy; 3) Active implementation of IMCI in the country and availability of trained health workers; 4) Strong JHU links with ministry of health staff and research institutions in the country; and 5) Availability of highly trained local research counterparts.

5.8 Clinical Efficacy of Short Course Treatment with Ceftriaxone for Bacterial Meningitis

Implementing Organizations: JHU/FHACS and WHO/CAH

Description: A multi-centre study will be set up in developing countries. Bacterial meningitis cases among children will be randomized to two treatment groups. One group will receive 5 days of injectable third generation cephalosporin (ceftriaxone or cefotaxime) followed by 5 days placebo in a blinded manner and the other group will be randomized to injectable third generation cephalosporin (ceftriaxone or cefotaxime) for 10 days. Cerebrospinal fluid and blood isolates will be obtained before treatment and after 24-48 hours of treatment to see the persistence of bacteria in the cerebrospinal fluid or blood. Facilities for CSF cultures and basic susceptibility testing will be developed where they are not available.

Countries/Regions: Guatemala, Pakistan, South Africa, and Vietnam (a total of ten tertiary care hospitals). WHO will conduct studies in Pakistan and South Africa; JHU will conduct studies in Guatemala: Hospital General San Juan de Dios (HGSJD); Hospital Roosevelt (HR); and the General Hospital of the Institute of Guatemalan Social Security (IGSS). (The HGSJD will be the coordinating center.) To get adequate number of patients which are representative would require at least 4-5 sites.

5.9 Development of a Clinical Prediction Instrument for Group A Streptococcal Pharyngitis (GRASP)

Implementing Organization: JHU/FHACS and WHO/CAH

Description: In many developing countries it is not possible to obtain a throat culture needed for identification of GRASP prior to the prescription of appropriate antibiotics. This collaborative, multi-center study seeks to improve the diagnosis and management of streptococcal sore throat by determining the clinical findings that reliably predict GRASP using standardized laboratory protocols. The goal of the study is to help clinicians make more rational use of the clinical history and examination in determining the need for antibiotic therapy. A second goal is to reduce the unnecessary use of antibiotics in patients having a low probability of streptococcal pharyngitis. Local capacity will be built by standardizing methodology for culture and serology.

Country/Regions: Possible sites include Brazil, Columbia, Eastern Europe (2), Egypt, India, Pakistan, United States, Zimbabwe.

5.10 A Multi-Center, Prospective, Observational Study of Clinical Outcome Following Amoxycillin Treatment of Non-Severe Acute Respiratory Infection

Implementing Organization: HIID/ARCH

Description and Countries/Regions: Strengthening individual and institutional and national research capacity is a major goal of the ARCH Project. This will be accomplished through workshops in proposal development and data analysis, and the provision of technical assistance. Last May, the ARCH Project, in collaboration with WHO/CAH, conducted a Protocol Development Workshop in Durban, South Africa to develop the severe pneumonia multicenter trial. A Data Analysis Workshop will be held in 1999. ARCH Project staff and consultants will serve as facilitators to assist with the analyses and writing draft manuscripts.

Countries/Regions: India, Peru, South Africa and Vietnam. (ARCH Project will only cover the Peru and South Africa sites).

5.11 Efficacy of Short Course Treatment with Oral Amoxicillin for Non-Severe Pneumonia and its Relationship with Antimicrobial Resistance

Implementing Organization: WHO/CAH

Description: The aim of this research is to optimize antimicrobial use for childhood diseases to slow the emergence and spread of antimicrobial resistance. In a multi-centre trial, non-severe pneumonia cases among children 2-59 month old will be randomized to two treatment groups. One group will be randomized to oral amoxicillin for 3 days followed by 2 days placebo in a blinded manner and the other group will be randomized to oral amoxicillin for 5 days. Nasopharyngeal isolates will be obtained before and after treatment to see the resistance levels of *S. pneumoniae* and *H. influenzae* to penicillin, cotrimoxazole, ampicillin etc.

Countries/Regions: Pakistan (total of 6 hospitals in Gilgit, Islamabad, Lahore, Multan, and Rawalpindi.)

5.12 Efficacy of Short Course Treatment with Oral Cotrimoxazole in Treatment of Non-Severe Pneumonia and its Relationship with Antimicrobial Resistance

Implementing Organization: WHO/CAH

Description: The aim of this research is to optimize antimicrobial use for childhood diseases to slowdown the emergence and spread of antimicrobial resistance. In a multi-centre trial, non-severe pneumonia cases among children 2-59 month old will be randomized to two treatment group. One group will be randomized to oral cotrimoxazole for 3 days followed by 2 days placebo in a blinded manner and the other group will be randomized to oral cotrimoxazole for 5 days. Nasopharyngeal isolates will be obtained before and after treatment to see the resistance levels of *S. pneumoniae* and *H. influenzae* to penicillin, cotrimoxazole, ampicillin etc.

Countries/Regions: Prospective sites include Bangladesh (Matlab) and Indonesia (Bandung). Discussions are underway with interested researchers.

5.13 Increased Specificity of Treatment Guidelines for Non-Severe Pneumonia

Implementing Organization: WHO/CAH

Description: In a multi-centre trial of non-severe pneumonia among children 2-59 month old cases will be randomized to two treatment groups. One group will be randomized to oral amoxicillin for 5 days and the other group will be randomized to oral placebo for 5 days. Blood cultures nasopharyngeal swabs for *S. pneumoniae* and *H. influenzae* and nasopharyngeal aspirates for RSV virus will be obtained in these children.

NOTE: The sample size needed to answer this question is much bigger study than what was anticipated before the proposal development workshop. It means that some sites would have to collect data for up to 18 months in order to get enough patients over two acute respiratory infection (ARI) seasons. It is expected that approximately one-third of this amount will be spent on microbiology and the rest on the clinical aspects of the study.

Countries/Regions: A descriptive study was conducted in Vietnam (Ho Chi Minh City) and South Africa (Durban). Potential sites for a larger study include Peru, Paraguay, Brazil, South Africa, and a few countries in Asia.

Year Started: FY1998 **Expected Completion:**

5.14 Increased Specificity of Treatment Guidelines for Children with Wheezing Diagnosed as WHO-Defined, Non-Severe Pneumonia

Implementing Organization: HIID/ARCH and WHO/CAH

Description: In a multi-centre trial of children 2-59 month old with wheeze assessed as non-severe pneumonia will be randomized to two treatment groups. One group will be randomized to oral amoxicillin for 5 days the other group will be randomized to oral placebo for 5 days. Blood cultures nasopharyngeal swabs for *S. pneumoniae* and *H. influenzae* and nasopharyngeal aspirates for RSV virus will be obtained in these children.

Countries/Regions: The study will be conducted in Argentina, Bangladesh, Brazil, Egypt, Gambia, India, Indonesia, Nigeria, Pakistan, Philippines, South Africa, and Thailand.

5.15 Clinical Efficacy of Oral Amoxicillin as Compared to Injectable Penicillin for the Treatment of Severe Pneumonia

Implementing Organization: HIID/ARCH and WHO/CAH

Description: In a multi-centre trial, severe pneumonia cases among 3-59 months old will be randomized to either therapeutic regimen. One group will be randomized to oral amoxicillin for 7 days and the other group will be randomized to injectable benzyl penicillin for 7 days. Nasopharyngeal swabs will be obtained from all patients to assess penicillin-resistant strains of *Streptococcus pneumoniae* and *Haemophilus influenzae*. NOTE: The sample size needed to answer this question is more than 1700 severe pneumonia patients. This is a much bigger study than what was anticipated before the proposal development workshop. It means that some sites would have to collect data for up to 18 months in order to get enough patients over two acute respiratory infection (ARI) seasons. This funding will be used for both clinical and microbiology work planned for this study.

Countries/Regions: The study will be conducted in South Africa (Departments of Paediatrics Child Health at University of Cape Town, Cape Town and University of Natal, Durban), Ghana (Kitampo Vitamin A Project (KIVAP), Kintampo), Zambia (Tropical Diseases Research Centre, Ndola), Colombia (Unidad de Epidemiologia Clinica, Faculdad de Medicina, Pontifica Universidad Javeriana Carrera, Bogota), Mexico (Division de Investigacion Medica, Instituto Nacional de Pediatria, Mexico), and a few countries in Asia (India, Pakistan, and Vietnam).

5.16 Management of WHO-Defined, Very-Severe Pneumonia

Implementing Organization: HIID/ARCH and WHO/CAH

Description: In a clinical trial, very severe pneumonia cases among 2-59 months old children will be randomized to two treatment groups. One group will be randomized to injectable chloramphenicol for 7 days and the other group will be randomized to a combination therapy of injectable penicillin and gentamicin for 7 days. Blood cultures will be obtained to document the aetiology and susceptibility patterns of etiologic agents. Nasopharyngeal swabs would be obtained to document carriage and resistance rates in children with very severe pneumonia.
Countries/Regions: Study sites include Bangladesh, India, Mexico, Pakistan, Yemen, and Zambia.

5.17 Epidemiological and Laboratory Assistance

Implementing Organization: CDC/NCID

Description: CDC epidemiologists have considerable international experience in development and evaluation of surveillance, investigation, and intervention programs. In addition, there is a long history of collaboration with WHO and other international organizations on issues related to child survival and antimicrobial resistance. Given this background, we propose CDC participate in the technical review of proposals and consult with other partners. CDC laboratory personnel can provide expert review and laboratory training at CDC or in the field.

Countries/Regions: As needed.

5.18 Evaluation of the Impact of Pneumococcal Conjugate Vaccine on Antimicrobial Resistant *Streptococcus pneumoniae*

Implementing Organization: CDC/NCID

Description: This project will involve carriage studies in children before and after the widespread introduction of pneumococcal conjugate vaccine. Such widespread introduction is anticipated to occur in the United States possibly as soon as early in 2000. Baseline carriage studies are available in Alaskan native populations. This proposal is to conduct pre- and post-marketing carriage studies in areas with high levels of drug resistance (e.g., Alaskan villages) or conduct carriage studies pre- and post-vaccination in a developing country setting where vaccine is not currently being studied but where high levels of resistance make such study compelling (e.g., various Asian countries). Field studies of carriage used in this project will pilot test the consensus methods for nasopharyngeal colonization detection of drug-resistant *S. pneumoniae* as well as conform to the standards proposed by the World Health Organization committee on carriage studies used in connection with vaccine trials. The project may also offer an opportunity for field testing of components of the USAID supported laboratory manual for resistance testing.

Collaborators will consider use of cluster-design for sequential assessments of pneumococcal carriage and will include collection of simple data elements regarding relevant confounders and/or risk factors for carriage of resistant pneumococci. Young children in the community will be followed up repeatedly to assess short and longer-term impact of pneumococcal vaccination on acquisition of resistant organisms. Characterization of the serotype, and on a subset, genotyping, of pneumococcal resistant isolates will also be performed, to determine replacement carriage by nonvaccine types, and possible capsular switching between serotypes among the resistant clones.

Countries/Regions: This study should be conducted in an area with substantial prevalence of penicillin and/or sulfa resistance among pneumococci in order to efficiently determine the impact of vaccination on reducing colonization of resistant organisms (e.g., Asia, Eastern Europe, Alaskan villages, SE United States). Alaskan villages may be the ideal setting because of the anticipated widespread introduction of conjugate vaccines in the United States before other sites, the availability of baseline data on resistance, the availability of ongoing laboratory-based surveillance for invasive disease, and the fact that Alaskan villages reflect developing country settings with very high rates of respiratory and invasive pneumococcal diseases.

5.19 Studies to Evaluate Behavioral and Policy Interventions to Improve the Use of Antimicrobials at the Household and Community Levels

Implementing Organizations: HIID/ARCH and RPM/MSH

Description: This activity will follow the model for research capacity building and successful proposal development that has been employed by ARCH/ADDR for many years, and which formed the basis for the work in the first phase of the drug use intervention initiative.

During the first year, a request for proposals will be circulated through the research networks of the partners and other related organizations. Pre-proposals will be reviewed independently by each partner, and priorities for support based on the collective results of these reviews. At least six research teams will be invited to attend a proposal development workshop at which the research ideas will be clarified and developed into a full proposal. These proposals will be reviewed by external reviewers, revised according to their comments, and, when acceptable, approved for funding.

The six studies will be implemented by the research teams by the end of the first year or early in the second year. The typical study of this type will be two years duration. Technical support will be provided as required during the process of study implementation, with at least one visit per year b technical experts to each study team.

During the third year, research teams will be invited to participate in a data analysis workshop. Initial analyses of data will be completed, and research teams will prepare policy briefs for disseminating results of their studies at a local and national level. The works will be revised for publication in national and international scientific journals in order to maximize the value of the lessons learned.

Countries/Region: Countries will be determined by the results of a competitive review of submitted proposals. It is expected that at least one country will be included from Asia, Africa, and Latin America.

5.20 Home Management of Neonatal Sepsis by Village Health Workers and the impact on Neonatal Mortality and Colonization with Antibiotic-Resistant Bacteria

Implementing Organization: JHU/FHACS

Description: The project will be conducted in two countries. In each country, communities will be randomized to control or intervention arms. Criteria for study sited selection include high rates of infant mortality and home delivery, poor access to health care, availability of VHWs and a minimum of 6000 live berths per year. With a baseline neonatal mortality rate of 50/1000, an individually-randomized study with 1605 newborns in each group would be sufficient to detect a reduction of 40% in the intervention arm. As this is a community-randomized trial, doubling the sample size should be sufficient to account for between-community variability. We anticipate enlisting 10-15 communities, and 3210 newborns, for each study arm in each country.

Baseline data to be collected during the first year will include: 1) neonatal mortality rates; 2) causes of neonatal deaths based on verbal autopsy reports; and 3) newborn care practices. VHWs from the intervention community will be trained in neonatal care, including the recognition and management of neonatal sepsis. To further improve neonatal survival, VHWs and Trained Birth Attendants (TBAs) in the intervention community will be instructed in:1) the recognition and management of complicated pregnancy; 2) appropriate hygiene during delivery and the immediate post-partum period; 3) neonatal

resuscitation; and 4) newborn warming.

After completion of the baseline data collection and training, VHWs will perform regular home visits in the intervention community on days 1, 3, 7, 14, 21 and 28. If the birth weight is less than 2500 grams, home visits will take place daily until one month of age. VHWs will be trained to diagnose neonatal sepsis using the following criteria: 1) temperature greater than 38 C or less than 36 C; 2) poor feeding; 3) lethargy; 4) erythema and tenderness around the umbilicus; 5) a combination of diarrhea, vomiting and/or abdominal distention; and 6) severe pneumonia. Parents of infants diagnosed with sepsis will be encouraged to take the child to the nearest hospital. If not feasible, the VHW will initiate antibiotic therapy. The antibiotic regimen will be parenteral ampicillin and gentamicin, or oral cotrimoxazole and parenteral gentamicin. The VHW will maintain a record of the daily clinical status and outcome for each infant diagnosed with sepsis. VHWs will visit newborn infants in the control community within 24 hours of birth. If the infant weighs less than 2,500 grams, the mother will be advised to take the infant to the nearest hospital or health care facility. The VHW will visit the home and weigh the infant again at one month of age. A trained health care worker will perform a verbal autopsy to determine the cause of death for all infants who die.

Colonization with antibiotic-resistant bacteria will be assessed in a sub-sample of one month old infants during the baseline data collection period and at the end of the intervention. Nasopharyngeal and stool/rectal swabs will be obtained from one month old infants and cultured for penicillin-resistant *Streptococcus pneumoniae* and ampicillin-resistant *Escherichia coli*. Costs will be recorded during the training and intervention periods, and categorized as service costs or research costs. Anticipated costs include training, equipment, wages, incentives, drugs, supplies and transportation.

Countries/Regions: Proposed sites include Mali, India, Nepal and Haiti.

5.21 Impact of IMCI Counseling Guidelines on Compliance with Antimicrobial Therapy in the Home

Implementing Organization: JHU/FHACS

Description: Study Site The study will be conducted in sikasso Region, Bougouni District, Mali. For the purposes of this study, Bougouni District can be divided into 3 zones.
Zone 1: This comprises two rural arrondissements and the commune (urban area) of Bougouni where Save The Children USA has implemented a USAID BHR/PVC Child Survival grant from September 30, 1995 to September 29, 1999. Activities implemented under the grant included immunization, improved case management of diarrhea and malaria in health centers and in the home, nutrition including Vitamin A distribution, family planning and maternal health. There were no specific intervention activities related to acute respiratory infections.
Zone 2: This comprises 3 rural arrondissements where the Save The Children project will be expanding its activities through mission funding from USAID/ Bamako after the current child survival project in Zone 1 ends.
Zone 3: This comprises 6 other rural arrondissements that are not included in either of the Save The Children projects.

Study Design	Time 1	Time 2	Time 3
Zone 1		M I	M
Zone 2	M I	M	

Zone 3 M

I=Intervention: Personnel in Health Centers receive a modified IMCI training course including the complete IMCI training on counseling of parents on how to administer the drug to the sick child.
M= Measurement: Measurement of reported doses of antimicrobials given in the home will be conducted. For children receiving antimicrobials for diarrhea or ARI at health facilities, home visits will be made after 5 days. Completion of the course of antimicrobials will be assessed by history and by counting antimicrobials remaining after 5 days. Exit interviews will also be conducted with a sample of parents of young children upon leaving the health facility. Respondents will be administered a brief survey about how long they waited, what happened in the appointment, what treatment they were told to take, etc.

Comparisons:
1) Comparison of Zone 2 at Times 1 and 2 and Zones 2 and 3 at Time 2 will show how much IMCI training of health personnel improves compliance in health facilities that had not otherwise been upgraded.
2) Comparison of Zones 1 and 2 at Time 2 will show how much better IMCI training is than the routine training implemented as part of many PVO child survival projects that include diarrhea and malaria case management.
3) Comparison of Zone 1 at Times 2 and 3 will show how much improvement results from IMCI training in facilities that have already had some upgrading.

Other data collection methods: A sample of 30 parents of young children will be administered a semi-structured interview on knowledge and perceptions of medications.

Countries/Regions: Save The Children USA is just completing a four year Child Survival Project (CS XI) (September 30, 1995 to September 29, 1999) in Bougouni District, Sikasso Region, Mali. Save The Children has developed local capacity to carry out operations research, and is eager to build on existing activities. While not providing funds, Save The Children will make some project resources available for the study.

5.22 Assessing The Effectiveness of Client-Based Job Aids to Support Compliance with Antibiotic Treatment Regimens

Implementing Organization: QAP II

Description: Determine scope: Select type of patients or caretakers. Determine scope of treatment plans (e.g. ARI among children). Assess client needs and problems: A brief formative study is undertaken to understand the needs of patients, the ability to use and read job aids, and additional support that can be provided by primary health providers.

Iterative testing of the job aid(s): QAP's quality design method (PETAL) is used to design the job aids, test the job aid with patients/caretakers, assess the results and receive feedback, then redesign and repeat the process until the job aid meets the needs of the patient or caretaker. The study will 1) measure improvements in correct use of antibiotics, as well as the patient's ability to effectively use the job aid, and 2) cost the of introduction and production of the job aid.

Countries/Regions: The study will be completed in an African country where QAP has already been working with local counterparts to develop and test job aids such as Malawi and Zambia.

5.23 Improving Knowledge of Primary Care Physicians and Medical Students to Enhance Rational Prescribing of Antimicrobials through the Use of Established Drug Information Centers and Networks

Implementing Organization: RPM/USP

Description: The proposed activity takes advantage of the ongoing RPM/USP activities in the Russian Federation and Moldova that relate to the provision of unbiased drug information. Specifically, the activities will build on the Russian translation/adaptation of the USP DI database and the establishment of the 12-member All-Russia Drug Information Network (ARDIN) and the Moldovan Association DRUGS. USP will work with members of ARDIN and the Moldovan Association DRUGS in the development of strategies for improving access to unbiased information about antimicrobial agents and in the creation of a training module for educating practitioners and students about their appropriate use. Concurrently, USP will work with PHARMEDINFO to publish a subset of the translated/adapted USP DI antimicrobial information monographs as an inexpensive reference for clinicians. The information will be condensed from the full monographs included in the Russian USP DI translation/adaptation. The format for the monographs will be developed through consultation with MOH officials and medical specialists, with input from ARDIN and DRUGS members. Where appropriate, local adaptations of the information will also be included in those materials developed for use in a specific geographic area. This process will not only serve to develop relevant, useful information but it will also raise awareness of the problem of antimicrobial resistance and build demand for appropriate training and the handbook. PHARMEDINFO will publish up to 20,000 copies of the handbook (depending on costs) and make them available for use in the training initiatives. It is anticipated that PHARMEDINFO will also make copies available at a subsidized rate for other clinical health care providers and will make the information available via electronic means, such as the Internet. The information will also serve as a resource for articles published in local and regional newsletters and bulletins that are developed by the drug information centers. Local and regional ARDIN members will coordinate use and evaluation of the teaching modules in their respective areas. After appropriate evaluation and revision, through a "training-the-trainers" approach, ARDIN members and the Association DRUGS will work to involve other information centers and institutions in Russia, Moldova, and potentially other NIS countries in effectively using the training module in their respective populations.

Countries/Regions: Russia, Moldova, and other NIS countries as determined appropriate and feasible; potential for replication in other developing countries.

5.24 Improving Patient Counseling and Dispensing Skills of Private Drug Retailers

Implementing Organization: RPM/USP

Description: *Progress to date* includes research that has been done with the private sector retailers on the dispensing of and patient counseling for antimicrobials during FY 99 using funds from the 1998 allocation of ID money. The Manoff Group was contracted to develop a research plan, manage data collection and analysis and present findings and recommendations for an appropriate intervention. Manoff has worked

in collaboration with New Era, a local Nepali research group. Preliminary results of the research show that:

- drug retailers dispense antibiotics for illnesses that do not necessarily call for antibiotic treatment;
- Drug retailers learn what antibiotics to dispense by observing what doctors prescribe for the same illness;
- Drug retailers do minimal, if any, labeling of medicines dispensed
- Drug retailers provide very little or no counseling to their clients when they dispense medicines to them;
- Drug retailers often sell less than the required/appropriate amount of antibiotics;
- To some extent, drug retailers see themselves as health care providers, not just businessmen;
- Drug retailers would welcome more training on drug selling;
- Drug retailers have very few, if any reference materials, and do not make effective use of those that they do have.

The findings from the qualitative portion of the research, which examines *why* the above findings are true, will inform the design and development of training and reference materials. For example, simple and easy-to-use reference materials on appropriate packaging and labeling may be indicated. In addition, support for drug retailers' encouraging clients to follow a full course of antibiotic treatment, instead of taking the medicine just until they feel better, may be appropriate.

In process: The training intervention is being developed and field-tested in collaboration with RPM/MSH. Core funds are being used to develop the draft training materials which can be adapted by other countries.

Planned for FY 2000: Core funds will also be used to develop a facilitator's guide for use by trainers of retailer-groups. Nepal ID funds will be used to evaluate the field test and revise the intervention and materials for Nepal. Additional core funds are requested to disseminate the training materials outside of Nepal as a model and to assist other countries with adapting/translating the model for local use through a sub-agreement mechanism. During FY 2000, the intervention will be evaluated and a rollout implementation phase will be planned. The group of drug sellers who go through the field-test training will be compared to a group of untrained drug sellers three months after the training. At the end of the field test, measures such as decreased AM drug sales, changes to more appropriate products, increases in repeat customers, improved patient/consumer counseling, will be used to evaluate impact. The DDA has already agreed, in principle, to include the training in the new requirements for drug retailer licensing being established now in Nepal.

Countries/Regions: Nepal

5.25 Methodology to Assess Malaria Drug Management in Developing Countries

Implementing Organization: RPM/MSH

Description: The rapid assessment methodology and indicators will build upon three existing RPM tools. The *Manual for Rapid Pharmaceutical Sector Assessment,* a tool for assessing the overall performance of a pharmaceutical sector, provided the foundation for the later development for the *Manual for Drug Management for Childhood Illness (DMCI).* The latter was designed to assess the specific drug management

concerns of countries considering implementing Integrated Management of Childhood Illness (IMCI) programs and for those with existing IMCI programs. The *DMCI* approach for assessing IMCI drug will be adapted to create a new tool for assessing the availability and the use of drugs to treat malaria. The third RPM tool that will be adapted for malaria drug management is the Cost Estimate Strategy (CES) tool. This tool, originally developed to assist Reproductive Health Programs, estimates drugs and commodities needs and corresponding costs, according to both actual and normative use patterns. The tool is particularly useful when considering expanding programs.

The *Drug Management for Malaria (DMM)* tool will follow the same developmental approach taken by the *DMCI* manual. The manual will discuss key drug management issues for the treatment of malaria, indicators for assessing the status of malaria drug management, their calculation, interpretation, and suggestions for follow-up actions. The assessment methodology will include a structured questionnaire instrument to be applied in both the public and private sectors to obtain data for conducting a cost comparison analysis, lead time analysis, availability of key drugs analysis, a review of prescribing, among others. The *CES* tool will be adapted to include the drugs and medical supplies required for the treatment of malaria as per existing national and international treatment guidelines, and will be incorporated into the assessment methodology. A comprehensive data collectors guide will be developed to accompany the manual.

The tool will be field tested in an appropriate setting. The purpose of the field test is to clarify concepts, language and presentation of the material, as well as finesse data collection issues. The field test will involve collaboration with local counterparts in the design, planning and implementation and follow-up review and analysis of preliminary results.

Countries/Regions: Africa (Tanzania is being considered as the site to field test the assessment tool)

5.26 Methodology to Assess Tuberculosis Drug Management in Developing Countries

Implementing Organization: RPM/MSH

Description: This tool will build upon three existing RPM tools. The *Manual for Rapid Pharmaceutical Sector Assessment,* a tool for assessing the overall performance of a pharmaceutical sector, provided the foundation for the later development for the *Manual for Drug Management for Childhood Illness (DMCI).* The latter was designed to assess the specific drug management concerns of countries considering implementing Integrated Management of Childhood Illness (IMCI) programs and for those with existing IMCI programs. The *DMCI* approach for assessing IMCI drug will be adapted to create a new tool for assessing the availability and the use of TB drugs. The third RPM tool that will be adapted for TB drug management is the Cost Estimate Strategy (CES) tool. This tool, originally developed to assist Reproductive Health Programs, estimates drugs and commodities needs and corresponding costs, according to both actual and normative use patterns. The tool is particularly useful when considering expanding programs.

The *Drug Management for Tuberculosis (DMTB)* tool will follow the same developmental approach taken by the *DMCI* manual. The manual will discuss key drug management issues for the treatment of TB, indicators for assessing the status of TB drug management, their calculation, interpretation, and suggestions for follow-up actions. The assessment methodology will include a structured questionnaire instrument to be applied in both the public and private sectors to obtain data for conducting a cost comparison analysis, lead time analysis, availability of key drugs analysis, a review of prescribing, among

others. The *CES* tool will be adapted to include the drugs and medical supplies required for the treatment of TB, as per existing national treatment guidelines and as per internationally recognized guideline such as the WHO DOTS program, and will be incorporated into the assessment methodology. A comprehensive data collectors guide will be developed to accompany the manual.

The *DMTB* tool will be distributed for external peer review with structured feedback mechanisms. After revisions have been completed to the tool as per the feedback, the tool will be field tested in an appropriate setting. The purpose of the field test is to clarify concepts, language and presentation of the material, as well as finesse data collection issues. The field test will involve collaboration with local counterparts in the design, planning and implementation and follow-up review and analysis of preliminary results.

Countries/Regions: Tool development will take place in Washington, DC. One country in either Africa or the NIS (yet to be determined) will be selected to field test this tool.

5.27 Increased Specificity for Treatment Guidelines for Clinical Overlap of Non-Severe Pneumonia and Malaria

Implementing Organization: WHO/CAH

Description: The study will be designed and implemented in an area with significant clinical overlap of malaria and pneumonia. Children between 2 and 59 months old who present with fever and fit the case definition of pneumonia will be tested for malaria using simple and quick diagnostic tests. This test will be compared with the presence of malarial parasites in peripheral blood.

Countries/Regions: The study will be conducted in an area with significant clinical overlap of malaria and pneumonia e.g. The Gambia, Kenya or Vietnam. Discussions are underway to select site.